REMARKS

Claims 1-6, 8-14, 17-19, 48, 50, 58 and 59 are pending in the instant application. Claim 1 has been further amended for clarity to indicate that the immune cells will encounter the antigen within the porous matrix of the device. Support for the amendment can be found at page 12, lines 10-15 and page 18, lines 10-13 of the specification. Thus, no new matter has been added by this amendment.

1. REJECTION FOR DOUBLE PATENTING

Applicants thank the Examiner for acknowledging their request to hold the double patenting rejections in abeyance.

2. THE REJECTION FOR OBVIOUSNESS UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

Claims 1-6, 8-14, 17-19, 48, 50, and 58-59 are rejected under 35 USC § 103(a) as being obvious in light of Barr et al. ("Barr"), U.S. Patent No. 5,593,697, in view of Andrianov et al. ("Andrianov"), U.S. Patent No. 5,529,777. The Office Action addresses the Applicants' previous assertions that Barr fails to render the present invention obvious because: (1) the two device induce an immune response in different manner, (2) Barr does not contain a diffusion barrier, and (3) the devices have different reasons for incorporating the polymers. The Office Action maintains that the two devices operate in a similar manner and by asserting that a diffusion barrier is actually present in the Barr device. The Office Action continues to rely upon *In re Spada*, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990) for the principle that products of identical chemical compositions can not have mutually exclusive properties in support of the assertion that Barr renders the current invention obvious given the suggestion that similar polymers may be used within the inventions. The Applicants respectfully disagree with the Office Action.

The Legal Standard

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the prior art references themselves or in

the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. 2143.

As the Applicants have asserted previously, the structure of the current device is not obvious from Barr. The claimed invention relates to a method of inducing an immune response by implanting a novel implant made of a porous matrix impregnated or injected with the antigen contained within a perforated but otherwise impermeable container that replicates the environment of a lymph node. (Page 4, Lines 12-15). The porous matrix provides for a reservoir for the antigen and the cytokines and other co-stimulatory factors to accumulate within the device and the perforated but otherwise impermeable container permits ingress and egress of immune cells while restricting the release of antigen, cytokines, or co-stimulatory factors from the device. The cumulative structure of the device acts as a diffusion barrier: maintaining within the device the antigen and high levels of cytokines and other co-stimulatory factors produced by immune cells that enter the device which in turn enhance the response of subsequent immune cells that enter the device. (Page 4, Line 21 to Page 5, Line 1).

In contrast, the Barr device is comprised of a solid core of (a) a biologically active material and (b) an excipient comprising at least one water soluble material and at least one water insoluble material coated with a continuous polymer film coating adapted to rupture at a predetermined time after implantation. (Col. 3, lines 30-42). This device provides for the administration of antigens in a pulse released fashion, in which the antigen contacts tissue in the host animal, at a period of time after implantation. (Col. 1, lines 7-11).

The device of Applicant's method claims is not obvious in light of Barr and Barr provides no motivation to one of ordinary skill in the art to modify the Barr device in accordance with the device of the Applicant's method claims. Specifically, the Barr device has a compressed solid core comprised of the biologically active material and excipients (col. 4, lines 28-33), whereas the device of the current method claims has a porous matrix. The pores within the porous matrix of the current device act as reservoirs for the antigen as well as cytokines and co-stimulatory factors released by the immune cells that enter the device. Contrary to the assertion in the Office Action, the immune cells would not be able to enter the compressed solid core of the Barr device. Thus, the

cytokines and co-stimulatory factors associated with the immune response would not accumulate within the Barr device and the enhanced immune response of the claimed method would not be achieved. One of ordinary skill in the art would not be motivated to replace the compressed solid core of the Barr device with the porous matrix of the Applicant's device given Barr's express disclosure of the use of "compressible excipients." *See* column 3, line 63-37. Further, given that Barr teaches that the core content is released as a pulse, col. 5, lines 12-18, one of ordinary skill in the art would not appreciate the need for a porous matrix to permit the accumulation of cytokines or co-stimulatory factors associated with the immune response within the Barr device.

The Office Action relies on *In re Spada*, 911 F.2d 705, 709 (Fed. Cir. 1990) for the principle that "products of identical chemical compositions cannot have mutually exclusive properties." However, the reliance on *In re Spada* appears inappropriate since it is the structural differences that differentiate the devices.

As noted above, Applicants' device consists of a porous matrix contained within a perforated container that generates a diffusion barrier permitting the concentration of antigen and co-stimulatory factors within the device while permitting the ingress and egress of immune cells. Whereas the Barr device provides a delayed pulse release of antigen by coating a compressed solid core in a continuous film that controls the timing of the delayed release of the core. The Office Action appears to assert that the current device and the Barr device are similar given that they are constructed of biodegradable materials and will eventually disintegrate thereby releasing their payloads. Such simplification ignores the essential difference in the structure and operation of the two devices.

The device of the current invention provides for a perforated container and a porous matrix. As noted within Example 2, Figure 2 and Example 15, Figure 20 of the current application, these structures permit ingress of immune cells into the device as well as the accumulation of cytokines and co-stimulatory factors within the device. The current invention also provides that this accumulation of antigen, cytokines, and co-stimulatory factors enhances the immune response of the immune cells within the device. This effect culminates prior to 10 days following implant after which the device can degrade. The release of antigen and any co-stimulatory factors from the device is negligible given that the immune response has already been induced. (Page 24, lines 2-4, and Example 3, Figure 3). The Barr device on the other hand is implanted with a continuous film

surrounding the compressed solid core. Even when the continuous film is permeated by physiological fluid, immune cells would not be able to penetrate the compressed solid core of the device. Barr discloses that it is advantageous for minimal release of antigen prior to the rupture of the device, and therefore there would not be an opportunity for cytokines and co-stimulatory factors to accumulate within the device. Thus, only upon degredation of the Barr device does a pulse release of the antigen occur to induce an immune response. In the current Application the device biodegrades after the immune cells have left the device, after the immune response is induced, whereas in the Barr the device biodegrades at the time it induces the immune response by releasing the antigen.

Lastly, contrary to the Office Action, the devices are not made of the same chemical compositions. Specifically, Barr discloses a compressed core of at least one water soluble excipient and one water insoluble excipient that contains the antigen. The water soluble excipient may be a sugar-based material such as lactose. (col. 3, lines 52-54) The water insoluble excipients of the Bar device serve two purposes: (1) to provide physical form to the implant when it hydrates, and (2) to provide a disintegrant which swells when hydrated to rupture the film coating of the Barr device. (col. 3, lines 56-60) Calcium phosphate and sodium starch glycolate are disclosed, respectively, as water insoluble excipients that serve those purposes. Barr indicates that "[t]hose skilled in the tabletting art will appreciate that other insoluble compressible excipients and swelling excipients (disintegrants) may be used." Col. 3, lines 65-67.

The device of the method claims of the current invention discloses a porous matrix of various polymers including hydroxylated polyvinyl acetate polyurethane, ethylene/vinyl acetate copolymer, polylactic acid, polyglycolic acid, polylactide-glycolide copolymer, collagen, cross-linked collagen, and gelatin. The current invention does not include the use of multiple excipients such as water soluble excipients or disintegrants. Given this difference in chemical composition it cannot be assumed that the core of the Barr device and the porous matrix of the device of the current method claims have the same or similar properties.

Applicants submit that, the current the obviousness rejection, is based upon, perhaps unconsciously, a hindsight reconstruction without taking into mind to the state of the art at the time of filing the present application. As stated above, such hindsight reconstruction does not meet the legal standard for obviousness. The reference cited by the Office Action does not suggest or provide

motivation for the presently claimed invention, let alone to do so with an expectation of success, as noted above.

Thus, the current invention would not have been obvious to one off ordinary skill in the art. The Office Action acknowledges that Barr does not teach the use of the device for generating hybridomas. However, the Office Action relies upon Andrianov to argue that would have been obvious to one of ordinary art to use the current invention to make hybridomas. As the Applicants' note above the current invention is not obvious in light of Barr and therefore the combination of Barr and Andrianov will not render the current invention obvious.

CONCLUSIONS

Applicants respectfully request that the foregoing amendment and remarks be made of record in the file history of the instant application. Applicants estimate that the remarks and amendment made herein now place the pending claims in condition for allowance.

Respectfully submitted,

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